Hemorrhagic Thrombocythemia: A Critical Review

By F. W. Gunz

HEMORRHAGIC thrombocythemia is a term first suggested by Epstein and Goede17 in 1934 as a suitable name for a disorder characterized by repeated hemorrhages, chiefly from the mucous membranes, and by a remarkable increase in the number of circulating platelets. Cases of this nature appear in the literature under a variety of names such as thrombocytosis, essential, idiopathic or primary thrombocythemia, megakaryocytic leukemia, and others. They are also reported as occurring in the course of granulocytic leukemia, polycythemia vera and myelosclerosis with myeloid metaplasia of the spleen (MMM); a tendency has lately arisen to include all these conditions in a single group, the myeloproliferative disorders.11,12 The individuality of hemorrhagic thrombocythemia has been questioned, some authors regarding it not as a distinctive disease but merely as a symptom complex which could arise in the course of a variety of conditions,4,7,15 while others consider it a definite entity.20,78

In this review two separate questions will be considered:

1. Is there a condition whose etiology and pathology are sufficiently distinctive to justify the term “primary” or “essential” thrombocythemia?

2. Whether or not “primary” thrombocythemia can be established as a pathologic entity, can cases be grouped together on the basis of similar clinical and hematologic manifestations, so as to justify their separation from other possibly related clinical conditions?

It will be submitted that the answer to the first question is in the negative, but that to the second in the affirmative: though there is no pathologic evidence permitting the separation of “primary” thrombocythemia from other forms of thrombocytosis, a case can be made for the recognition of the clinical syndrome of hemorrhagic thrombocythemia.

DEFINITION

Hemorrhagic thrombocythemia is a clinical syndrome with the presenting symptom of recurrent spontaneous hemorrhages, either external or into the tissues, and often preceded or accompanied by thromboses in the superficial or deep veins. There is splenomegaly in the majority of cases. The hematologic findings are an extremely high platelet count and usually a high neutrophil leukocytosis. Anemia is generally present and often hypochromic, but there is a tendency towards mildly polycythemic red cell counts in the intervals between hemorrhages.

The discussion of this syndrome will be based on a consideration of five personal cases, and of reports of 50 cases drawn from the literature which comprise the bulk of those reported to date. Cases selected included all those
HEMORRHAGIC THROMBOCYTHEMIA: A CRITICAL REVIEW

complying with the above definition, with the exception of a number in which the thrombocytosis appeared to be a mere transient phase in the course of other well substantiated diseases. A history of hemorrhage was essential for inclusion. Either thrombocytosis or thrombosis without hemorrhage was insufficient; for example, cases 1 and 2 reported by Fanger et al.19 were included, while case 3 was excluded because the patient had not bled. A diagnosis of “essential” or “idiopathic” thrombocytosis was not acceptable for inclusion, unless hemorrhage was also reported. Cases excluded for this reason comprise those of Arlotti and Ballerini1 (case 4), Owren,25 Paraf et al.,26 Jasinski,31 Kissel et al.,32 Baikie et al.,1 (case 1), Lemaire et al.,33 Thieffry et al.,73 and Rowlands and Vaizey41 (case 2). A definite history of leukemia excluded a case (e.g., case 4,26 and the patients reported by McCabe et al.47 and Lebon et al.41), as did a strong history of polycythemia vera with episodic thrombocytosis (Moolten et al.,43 case 2; Baikie et al.,1 cases 2 and 3; Baserga et al.72) or of MMM (Marchal et al.,40 case 2; Arlotti and Ballerini,2 cases 2 and 3). The cases of the following authors were selected for analysis: Akazaki and Hamaguchi,2 Bigelow4 (cases 1 and 2); Binswanger et al.,5 Bousser,9 Brugsch,10 D’Antuono,14 Drake,16 Epstein and Goedel,15 Fanger et al.19 (cases 1 and 2); Forssell,20 Fountain21 (cases 1 and 2); Goudemand and Hutin,23 Hardisty and Wolff29 (cases 1-3 and 5); Hermann,27 Holst,28 Jackson et al.,30 Kupfer et al.,36 Lachnit,37 Laporte et al.,38 Lebel,10 Lemaire et al.,44 Levin et al.,45 Levinson et al.,46 Maupin et al.,51 Moolten et al.,54 (case 3), Mortensen,55 Reid,61 Revol62 (cases 1 and 2), Rowlands and Vaizey64 (case 2); Schüpbach and Hermann65 (case 1), Siede,66 Smith,67 Söderström,68 Spaet et al.,72 Spangberg and Zettergren,73 Stenström74 (cases 1-3), Uotila,77 Wasserman et al.,78 (cases 1-3), Woodrow and Cope.79

PERSONAL CASES

Case 1

Male, 40, Accountant. Splenectomy, excessive bleeding, transient polycythemia with thromboses, hypochromic anemia, death from hemorrhage.

8/17/48: Admitted for one week’s pain, worse on coughing in the left hypochondrium. Afebrile and not in distress. Mass in the left upper abdomen, extrinsic filling defect of stomach. Blood: anemia, leukocytosis (total 17,000/cu.mm., P 75 per cent), platelets “normal” in stained films. No diagnosis was made, but at laparotomy the abdominal mass was identified as the spleen and removed.

Postoperatively there was persistent bleeding from the wound, which greatly delayed healing. The removed spleen when fixed measured 13 x 9 x 9 cm, and showed multiple infarcts and many dense adhesions. The infarcts appeared to be “at least of some days, and some parts of several weeks duration.” Histologically no specific features were present. Ten days after operation the blood count showed HCT 25 per cent, WBC 45,000/cu.mm. (P 91 per cent), and platelets 1.8 million/cu.mm.

After six months without symptoms, the patient suffered repeated thromboses of the superficial (but not deep) veins of both legs. Hb now 21 Gm. per cent, WBC 30,000/cu.mm. (P 84 per cent). 10/6/52: Readmitted for investigation of iron deficiency anemia. Tongue sore and bald, nails spoon-shaped. Hb 7.5 Gm. per cent, HCT 26 per cent, MCHC 29 per cent, WBC 62,000/cu.mm. (P 96 per cent). The platelets were not counted but were numerous in films. Marrow hyperplastic and “consistent with iron deficiency anemia.” There was a histamine-fast achlorhydria, but no cause for the anemia was found.

8/1/53: Readmitted for melena. Bleeding continued for the next four weeks, and the
Fig. 1.—Case 1. Thromboplastin generation test showing deficient thromboplastin generation. Control and patient's platelets in equal concentration of $3 \times 10^6$ cu.mm.

Patient was given numerous blood transfusions. On 8/4/53 a large spontaneous retroperitoneal hematoma was found, which grew and led to a temporary ureteral obstruction. 8/27/53: Severe bleeding from a small ulcer of the mouth. Liver much enlarged. Full investigations are listed in table 1. The following months brought further bleeding from various sites, either spontaneously or after slight trauma. Death occurred on 7/12/54 after a sudden collapse with all the signs of a severe internal hemorrhage. Permission for an autopsy was not obtained.

Case 2

Female, 53, skein winder. Venous thromboses, threatened gangrene of toes, excessive bleeding, splenomegaly.

Admitted 7/27/58 because of incipient gangrene of the right fourth and fifth toes. Two year history of repeated venous thromboses in both legs. Large spontaneous hematoma of the left thigh. Severe epistaxis six weeks before admission. The patient was known to be hypertensive.

She was found to have a blood pressure of 210/120 mm. Hg. The right fourth and fifth toes were dusky red and showed early gangrene, but all arterial pulses were normally present. A lumbar ganglion block improved the warmth of the limb but not the appearance of the incipient gangrene. The spleen was felt 3 cm. below the costal margin. The results of laboratory investigations are detailed in table 1. The patient was treated with P₃₂₂ and busulphan, following which the condition of the foot improved and its circulation became...
HEMORRHAGIC THROMBOCYTHEMIA: A CRITICAL REVIEW

Table 1.—Hematologic Findings, Cases 1 to 5

<table>
<thead>
<tr>
<th>Test</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, Gm.%</td>
<td>7.5–21</td>
<td>8.5–16</td>
<td>9.0–15.5</td>
<td>7.0–14</td>
<td>4.5–?</td>
</tr>
<tr>
<td>HCT, %</td>
<td>—</td>
<td>31–49</td>
<td>30–52</td>
<td>24–43</td>
<td>—</td>
</tr>
<tr>
<td>RBC, Hypochromia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>WBC/cu.mm. × 10^3</td>
<td>70–112</td>
<td>22–35</td>
<td>23–43</td>
<td>17–80</td>
<td>29–80</td>
</tr>
<tr>
<td>Neutro. alk. phosphatase</td>
<td>—</td>
<td>—</td>
<td>++</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>RBC osm. frag.</td>
<td>—</td>
<td>N</td>
<td>—</td>
<td>—</td>
<td>N</td>
</tr>
<tr>
<td>Erythroblasts (blood)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>++</td>
</tr>
<tr>
<td>Myelocytes (blood)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>++</td>
</tr>
<tr>
<td>Total red cell mass</td>
<td>—</td>
<td>D+</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Platelets per cu.mm. × 10^6</td>
<td>2–6</td>
<td>1.1–3.4</td>
<td>0.8–2</td>
<td>1–1.8</td>
<td>Too many to count</td>
</tr>
<tr>
<td>(direct method)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plt. abnormality</td>
<td>N</td>
<td>+</td>
<td>N</td>
<td>N</td>
<td>N+</td>
</tr>
<tr>
<td>Plt. survival</td>
<td>—</td>
<td>N</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>++</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N+</td>
</tr>
<tr>
<td>Clotting time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Lee and White)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Prothrombin index (Quick)</td>
<td>40%</td>
<td>N</td>
<td>50%</td>
<td>42%</td>
<td>D</td>
</tr>
<tr>
<td>Clot retraction</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Thromboplastin generation</td>
<td>D</td>
<td>D N</td>
<td>N</td>
<td>N D</td>
<td>—</td>
</tr>
<tr>
<td>(Fig. 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulating anticoagulant*</td>
<td>—</td>
<td>N</td>
<td>+</td>
<td>N</td>
<td>—</td>
</tr>
<tr>
<td>Serum serotonin*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum uric acid (mg.% )</td>
<td>—</td>
<td>3.4</td>
<td>—</td>
<td>—</td>
<td>8.5</td>
</tr>
</tbody>
</table>

N = normal; + = increased; D = diminished; — = not tested.


†Serum serotonin estimation by Dr. F. S. Bigelow, Boston. Result of test previously published in reference 6.

normal. No further thromboses or hemorrhages occurred; the further hematologic findings are shown in figure 2.

Case 3

Female, 74, retired nurse. GI bleeding, splenomegaly.

Admitted 11/20/58 because of melena of three days' duration. Three years previously she had had indigestion and was said to have had a peptic ulcer. Since then many tarry stools and frequent upper abdominal discomfort. Some loss of weight. There was hepatomegaly, and a firm spleen was felt 3 cm. below the costal margin. No other abnormalities were found, and the bleeding subsided after a few days in bed. X-rays showed no peptic ulcer. Results of investigations are listed in table 1. She was treated with P32, and no symptoms recurred. Six months after admission there was a mild polycythemia (total red cell mass +36 per cent).

Case 4

Male, 79, retired farmer. Hypochromic anemia, bleeding tendency, splenomegaly.

Admitted 5/6/58 because of symptoms of anemia. He had been treated for pernicious anemia for 10 years, but there was no evidence to substantiate this diagnosis. Long history of osteoarthritis of the hips, for which he had received radiotherapy in 1950, 1953 and 1954.
He tended to bleed excessively and had frequent epistaxes. Shortness of breath on exertion, weakness and "racing" of the heart for the past 10 days. Examination showed pallor but no other obvious abnormalities, apart from restricted movements in both hips. X-ray showed a probably enlarged spleen. Results of investigations are listed in table 1. The patient was transfused and given prednisone. Two weeks later a brisk gastrointestinal hemorrhage occurred, and the prednisone was withdrawn. With busulphan and oral iron treatment, bleeding did not recur, and the blood count became and remained normal.

Case 5

(History and findings through the courtesy of Drs. M. R. McLean and J. O. Mercer, Wellington, New Zealand.)

Male, 30. Splenectomy, excessive bleeding, hepatomegaly, gout, death in uremia.

Admitted November, 1945 with splenomegaly. The spleen was removed, but no histologic sections or report survived.

May, 1946 and September 1947: Symptoms of anemia. Hb 4.5 Gm. per cent, RBC 1.6 million cu.mm., RBC stain poorly and show polychromasia. WBC 56,000 cu.mm. (F 85 per cent); 21 erythroblasts per 100 WBC. Platelets increased in films. Liver greatly enlarged. Transfused.

February, 1949: severe hemorrhage following tooth extraction. 1955: Melena, which he now stated to have been occurring for the past seven years. Hypochromic anemia, leukocytosis as before. "Enormous numbers" of platelets in blood films.

September, 1957: hematemesis traced to a prepyloric ulcer (Barium meal). Liver extremely large. Further admission in September, 1958 for anemia. Details of blood findings are shown in table 1. In March, 1959 he developed gout (serum uric acid 8.5 mg. per cent) and soon afterwards uremia from which he died.

Autopsy.—Body emaciated. Heart showed left ventricular hypertrophy. Lungs edematous. Liver enormously enlarged (weight 4700 Gm.), smooth, firm, uniform grey color. Discrete enlarged abdominal lymph nodes, especially in upper part of abdomen, grey color. Scar of old duodenal ulcer. Right kidney larger, left smaller than normal; both showed thickening and yellow striation of cortex. Bone marrow "prominent" and perhaps abnormally grey. Microscopically gross extramedullary hematopoiesis in liver and lymph nodes, with many megakaryocytes. Some hematopoiesis and advanced pyelonephritis in kidneys.
HEMORRHAGIC THROMBOCYTHEMIA: A CRITICAL REVIEW

ANALYSIS OF FINDINGS

Pathology of Hemorrhagic Thrombocytopenia. Is There a “Primary” Thrombocytopenia?

The visceral lesions of the condition are poorly described. When death occurred, it was caused either by uncontrollable hemorrhages (personal case 1), by thromboembolic phenomena, or by intercurrent disease (pyelonephritis: personal case 5; chronic nephritis; pneumonia; miliary TB; Ca stomach).

Bone marrow.—In all cases with autopsy findings, the marrow was wholly or partly hyperplastic, with a gross increase in the megakaryocytes. Occasionally some areas of the marrow were found to be fibrotic. Marrow biopsies in 4 of 5 personal and in 41 of 44 other patients showed some hyperplasia of the aspirated material, affecting the megakaryocytes in every case, nearly always with excessive numbers of often clumped platelets. Immaturity and structural abnormalities of some of the megakaryocytes were often noted, but many normal ones were always present. There was usually hyperplasia of the myeloid series, and often of the erythroid series. One personal case (no. 3) and one from the literature showed myelofibrosis in biopsy specimens. Two marrows were reported as normal.

The spleen.—The spleen was enlarged in all personal and in 40 other cases. The enlargement ranged from a minimum to very gross degrees. In most cases, however, the size was 2 to 4 times that of the normal organ. Two spleens were atrophic and one was calcified. In two personal and 13 other cases an enlarged, and in one case an atrophic spleen was surgically removed. Splenic infarction with splenic vein thrombosis appeared to be the commonest immediate reason for the operation. Histologically, the changes were described as “congestive” or those of “morbus Banti” in one personal and 8 other cases. Myeloid metaplasia was found in 3 cases at splenectomy, in two at autopsy, and in one by splenic puncture. The size of the spleen appeared unrelated to its involvement by myeloid metaplasia.

Myeloid metaplasia of organs other than the spleen was described in a few cases (liver, lymph nodes, kidney: personal case 5; liver), though in others there was little sign of it. The frequent enlargement of the liver which occurred following splenectomy suggests that myeloid metaplasia may have been more widespread than was indicated by histologic reports.

Thromboses of various blood vessels were diagnosed during life or after death, the commonest site being the splenic vein, with infarction of the spleen the consequence. No abnormalities of the thrombosed vessels were described. In one fatal case thrombocytopenia was associated with an unusual pulmonary intra-alveolar exudate.

Discussion.—The synonymous diagnoses “primary,” “idiopathic” or “essential” thrombocytopenia occur 15 times among the 50 cases analyzed. Such terms must imply the absence of other disease anteceding the onset of thrombocytopenia and responsible for its occurrence. When a rise of the platelet count is found in the course of conditions like hemorrhage, infections or malignant disease, the phenomenon is clearly secondary to them. It tends
to be transient, comparatively modest in size and unproductive of symptoms, and, following the suggestion of Di Guglielmo, is best termed thrombocyto-
sis, the designation of thrombocythemia being reserved for cases of a more
prolonged and pronounced increase in the platelet level (at least three times
the normal level, according to Leitner). Such high counts are found in some
cases of polycythemia vera and MMM, very occasionally in chronic granulo-
cytic leukemia, and sometimes following splenectomy. According to some
authors there is also a further small group of cases in which thrombocythemia
occurs unassociated with other diseases. This is the group termed "primary"
thrombocythemia.

In order to substantiate the existence of such a group, it must be shown
that it has a pathologic picture of its own. This is clearly difficult in many of
the cases under discussion. The great majority showed marrow hyperplasia,
the appearance of the myeloid and particularly the megakaryocytic series
being virtually indistinguishable from that known since the time of Osler to
be characteristic of polycythemia vera. Extramedullary hematopoiesis occurred
in some and resembled that found in MMM. Myelofibrosis was found on
several occasions. There is obviously a close family likeness between these
cases of "primary" thrombocythemia, polycythemia vera and MMM; the
difficulty of distinguishing between the pathologic findings in these myelo-
proliferative disorders has been clearly demonstrated.

The position of splenectomy in the etiology of "primary" thrombocythemia
is of particular interest. Of 15 removed spleens three showed myeloid meta-
plasia and nine the "congestive" changes of the Banti syndrome with or
without infarction. Rosenthal found in 1925 that in a small proportion of
patients splenectomized for "Banti's disease" the operation produced no
benefit but was on the contrary followed by the onset of recurrent thromboses
and hemorrhages with hypochromic anemia and a rise in the platelet count
which was greater and more sustained than in the remaining cases. These
patients had normal or slightly raised platelet counts before operation, and
Rosenthal termed them the thrombocythemic group.

The nine cases referred to above were evidently of the same type as those
mentioned by Rosenthal. In two of them the platelet count was said to
be normal and in two others elevated before the operation. In the rest
no preoperative platelet counts were made, but it seems likely that in most
if not all a preoperative thrombocytopsis existed, as in Rosenthal's patients;
splenectomy probably aggravated but did not produce it.

"Banti's disease," now commonly known as congestive splenomegaly, is
generally the consequence of hepatic cirrhosis. Only one of the 55 cases
under consideration was known, however, to have cirrhosis; in most of the
others the cause of the "congestive" splenomegaly was thrombosis of the
splenic vessels. This did not result from disease of the vessels, except in a
single case, but from the thrombocytopsis which probably existed before the
removal of the spleen. Thus thrombocytopsis, splenic enlargement and splenic
vein thrombosis existed in those cases which came to splenectomy and
showed no myeloid metaplasia. These are common findings in polycythemia
HEMORRHAGIC THROMBOCYTHEMIA: A CRITICAL REVIEW

vera, and thus thrombocytemia and polycythemia appear to be contiguous at yet another point. It is concluded that no sharp distinguishing line can be drawn between these two conditions.

In summary, there is no evidence to show that a pathologic picture exists capable of characterizing cases of “primary” thrombocytemia, but there are the closest affinities between it and certain members of the group of myeloproliferative disorders, especially polycythemia vera and MMM. It follows that any designation such as “primary,” “idiopathic” or “essential” is misleading, and that hemorrhagic thrombocytemia should itself be regarded as one form, or possibly one phase of a multifaceted myeloproliferative disorder, rather than as a distinct entity.

The Clinical and Hematologic Picture of Hemorrhagic Thrombocytemia

Among the 50 patients with hemorrhagic thrombocytemia there were 23 males and 26 females. The sex of one patient was not stated. The mean age was 51; there were 3 patients under 30, 17 between 30 and 50, and 30 above 50.

Symptoms.—The commonest symptom was bleeding, which occurred in all cases. This was spontaneous in onset, repeated and of very varying severity. The longest history of such hemorrhages extended over 27 years, another over 17 years, and many others over one to five years. Gastrointestinal bleeding was commonest. Less often there was hematuria, excessive bleeding after minor trauma, dental extractions or operations, hemoptysis or menorrhagia. Spontaneous bruising often occurred; at times extremely large hematomata formed after insignificant trauma. Purpura was never seen. In 11 cases bleeding first began after splenectomy, usually within a few months.

Thrombosis was demonstrated or suspected in 17 cases. The commonest site was the splenic vein; others were the superficial and deep veins of the legs and the veins of the penis (priapism); the latter complication occurred twice.

Enlargement of the spleen was the commonest abnormal physical sign and was reported in all personal and 40 other cases. In 8 reports the spleen was stated to be normal in size, and in two the size was not mentioned. The liver was enlarged in at least 17 cases. Peptic ulceration was proved in 8 cases and suspected in several others without confirmation. One patient had carcinoma of the stomach, and several had tuberculosis. Gout occurred in one personal and one other case.

Hematologic findings.—The platelets were much increased in number in every case. Counts were carried out by a great variety of methods, and their accuracy is occasionally doubtful. The highest counts recorded for each patient ranged from 0.9 to 14 million per cubic millimeter, mean 3.2. The platelet morphology was very often abnormal, with many irregular and distorted shapes, giant forms, chains, etc. Platelet agglutinates in films of blood or marrow were generally described as unusually large, and marrow specimens were in several cases said to consist chiefly of clumped platelets.
Leukocytes.—There was nearly always a considerable leukocytosis. An example is shown in figure 2, and the maximum counts recorded are listed in table 2.

The rise in the leukocyte count was always produced by a specific increase in polymorphonuclear neutrophils, and there were never more than 1 to 3 per cent of myelocytes or myeloblasts. A moderate eosinophilia was sometimes recorded. The mononuclear cells were normal. The neutrophil alkaline phosphatase level was very high in cases 3 and 4 of the personal series (no others tested).

Red cells.—Anemia was present at some stage of the disease in all personal and 32 other cases. No anemia was present in 12 cases, and no data were reported in 6 others. The anemia was definitely hypochromic in most instances. Its degree was very variable and depended on the extent of the preceding hemorrhage. Polycythemic red cell levels were found in 17 cases; they were never extremely high (highest RBC count 6 to 7 million per cubic millimeter, highest Hb 130 per cent), and no patient consistently showed polycythemia; anemia always alternated with polycythemia (fig. 3). The red cells were normal in shape in many cases, but in some there was considerable poikilocytosis.

Blood coagulation studies are considered in the analysis of the mechanism of hemorrhage (see below). Red cell osmotic and mechanical fragility, Coombs tests, liver and renal function, and serum electrolytes were normal when examined. The serum uric acid was occasionally raised.

Discussion.—It was shown in the preceding section that there is no distinctive pathologic picture characteristic of “primary” or “essential” thrombocythemia. The question now to be discussed is whether a clinical picture exists capable of characterizing a distinctive syndrome of hemorrhagic thrombocythemia.

There is no doubt of the close clinical similarity of this group of cases to other myeloproliferative disorders, especially polycythemia vera and MMM. All of them show the same age and sex incidence, splenomegaly and what may be termed a panmyelosis, with hyperplasia of all hematopoietic cells, and varying degrees of extramedullary hematopoiesis. Further indications of their intimate relationship may be found in the high level of neutrophil alkaline phosphatase, their frequent association with peptic ulceration, and the occasional complication of gout. Opponents of the concept of “thrombocythemia” as a separate entity point to the high platelet levels and

Table 2.—Maximum Leukocyte Counts (Thousands per Cubic Millimeter) in 45 Patients with Hemorrhagic Thrombocythemia

<table>
<thead>
<tr>
<th>Count</th>
<th>Number</th>
<th>Count</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>2</td>
<td>30-39</td>
<td>5</td>
</tr>
<tr>
<td>10-19</td>
<td>16</td>
<td>40-49</td>
<td>5</td>
</tr>
<tr>
<td>20-29</td>
<td>8</td>
<td>50-59</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60+</td>
<td>3</td>
</tr>
</tbody>
</table>

Average: 30,000 cu.mm.
hemorrhagic phenomena which may occur in otherwise unremarkable cases of polycythemia vera, leukemia or MMM.

While these similarities can be readily admitted, there are highly individual features, both clinical and hematologic. Chief among these is hemorrhage which dominates the picture. The condition is first and foremost a hemorrhagic disease, and the degree and duration of the bleeding is closely correlated with the platelet level: when bleeding occurs, the platelet level is high; when the latter falls to normal, bleeding ceases. Although bleeding is also reported to be a common manifestation of polycythemia vera, it is not quite logical to stress the polycythemic element in such cases, which like hemorrhagic thrombocytopenia show high platelet counts and hemorrhages as their leading features. Symptoms due to excessive blood volumes are on the other hand inconspicuous in both groups. Thus there is little complaint of headache, dizziness, visual disturbances, cardiac symptoms, itching, pain or paresthesias of the limbs which are so common in typical polycythemia. It seems rational to collect as one variety of the myeloproliferative disorders

![Diagram of blood volume changes](image-url)
all those cases with thrombocytosis and hemorrhage, and as another those with polycythemia as the chief manifestation.

Thrombosis occurred in the patients with hemorrhagic thrombocythemia, but relatively rarely. Apart from splenic vein thrombosis—a rather characteristic manifestation of this syndrome—few major vessels were involved. One patient died from a pulmonary embolus, one from portal vein thrombosis and one from a “heart attack.” This relative paucity of serious thromboembolic phenomena contrasts with the frequency with which they complicate classical cases of polycythemia vera.

McCabe et al. suggested that in many cases reported as (hemorrhagic) thrombocythemia the time of observation was too short to exclude the possibility of other primary disease. While this was true of several of the 13 cases analyzed by these authors, many patients in the present series had very long histories (see above). Moreover, unless splenectomy had been performed, the clinical course was often relatively stable over long periods, being punctuated by occasional hemorrhages, but with few signs of polycythemia. Most patients, especially when suitably treated, appeared to have an expectation of life of at least several and probably many years, the only danger being hemorrhage which would occur with a rising platelet count. Splenectomy nearly always produced a dramatic deterioration in the condition, with striking exacerbations in the hemorrhages, and converted a naturally very chronic into an acute and sometimes a fulminating disorder.

The hematologic features of hemorrhagic thrombocythemia are highly characteristic. An excessive elevation of the platelet count, often associated with abnormalities of the clotting mechanism (see below), is nearly always accompanied by extremely high counts of neutrophil polymorphonuclear leukocytes, as well as by an anemia, often hypochromic in nature. This trinity of blood abnormalities is found in no other condition. The absence of immature leukocytes differentiates it from granulocytic leukemia (although some of the cases in the literature were so regarded by their authors). While any one or two of the abnormalities may be found in cases of polycythemia vera or MMM, all three do not occur together. Hemorrhagic thrombocythemia must be distinguished from the very rare cases of genuine megakaryocytic or megakaryoblastic leukemia which are acute in course and characterized by the appearance in the blood of many primitive cells, including those of the megakaryocytic series with, or more usually without a thrombocytosis. These are closely related to acute granulocytic leukemia.

In summary, there appear to be sufficient clinical and hematologic features to characterize a distinctive clinical syndrome of hemorrhagic thrombocythemia which, like polycythemia vera or MMM, appears to be one clinical form of an underlying myeloproliferative disorder. Each of these groups tends to have a distinctive history and prognosis. At the same time transitions between all forms of the myeloproliferative disorders are common, and in many individual cases the classification must be one of personal preference.
HEMORRHAGIC THROMBOCYTHEMIA: A CRITICAL REVIEW

The Mechanism of Excessive Hemorrhage

The apparent paradox of excessive bleeding in the presence of excessive numbers of platelets has been remarked upon by many authors, and several rather full reviews have been published. Since no conclusive answer has been obtained, the question will be treated only summarily, further details being available by reference to the above papers.

The platelets.—The single certain fact concerning platelet structure or function is the 100 per cent correlation of excessive bleeding with high platelet levels: when bleeding occurred, the platelet level was found to be excessive. However, not every patient with a high platelet level bled. In a group of cases termed "essential thrombophilia" there was thrombosis as the leading symptom, hemorrhage was absent, the thrombosed vessels were said to be normal, and platelet counts were often very high. In the hemorrhagic group, there was no correlation between the height of the platelet level and the severity of bleeding: in a well authenticated case...
In a very recently published paper Alfos et al. (Lancet 2:941, 1959) report an increased in vivo life span of platelets in 3 cases of thrombocythenia.

The patient was known constantly to have a count of 10 to 14 million platelets per cubic millimeter over a period of five years but led a normal life throughout this period.

The platelets were often but not always reported as having an abnormal morphology. Their physiologic status also appeared uncertain. The platelet survival time in vivo seems to have been determined only once (fig. 5) and was then found to be normal. Their thromboplastic functions as ascertained by the thromboplastin generation test (TGT) was either normal, increased or decreased. It varied from patient to patient, and sometimes in the same patient. Soulier et al. tested 27 patients and arranged the results in four groups: (1) thromboplastin generation normal or increased with platelet concentrations the same as in vivo, remaining or becoming normal with dilution of the platelets to the control level; (2) thromboplastin generation normal with “in vivo” concentrations, subnormal with dilution; (3) thromboplastin generation subnormal with “in vivo” concentration, abnormality accentuated by dilution; (4) thromboplastin generation subnormal with “in vivo” concentration but becoming normal on dilution to normal levels. Equally variable results were obtained in patients 1 to 4 of the personal series (figs. 1 and 4). In Soulier’s group 4, the normalization of a subnormal thromboplastin generation after dilution of the platelets to normal levels could only be explained by the liberation of an anticoagulant by high concentrations of platelets. The existence of such an anticoagulant has been shown by others with high in vitro concentrations of normal as well as pathologic platelets. Its relation to clinical hemorrhage is not clear.

*In a very recently published paper Alfos et al. (Lancet 2:941, 1959) report an increased in vivo life span of platelets in 3 cases of thrombocythenia.
The platelet and serum serotonin (5-hydroxytryptamine) content were found to be diminished in case 1 of the personal series and in several other patients with hemorrhagic thrombocythemia, but the incidence of bleeding was unrelated to the mean platelet serotonin, and less critically related to the whole-blood (or serum) serotonin than to the platelet count. Since the source and significance of platelet serotonin is still unknown, its role, if any, in coagulation is problematic.

Other tests of the coagulation mechanism.—The bleeding time was exceedingly variable in both the personal and other cases. It was raised in cases 1 and 5, normal in cases 2 to 4; raised in 20, normal in 22 and not stated in 8 cases in the literature. Often the test changed from normal to abnormal in the same patient, or vice versa. There was only slight correlation between the abnormality of the bleeding time and severity of bleeding.

The capillary resistance was normal save in a single case. The coagulation time was always normal, as were the prothrombin consumption and clot retraction, although the clot when formed sometimes broke up prematurely. The Quick one-stage prothrombin activity was very often slightly decreased, and there are numerous reports of mild deficiencies in prothrombin, as well as factors V and VII, and a single case of AHG deficiency. A circulating anticoagulant was found in case 3 of the personal series, and one other case. A mild diminution in the plasma fibrinogen level was occasionally reported, but fibrinolysis was not observed. French authors recorded the presence of increased heparin tolerance in some instances, although the significance of this finding is not certain, in view of the difficulties of the test. Thrombelastographic studies showed the typical “bottle-neck” pattern of hypercoagulability.

Apart from the high platelet counts, there was thus no consistent pattern of abnormalities of hemostasis or blood coagulation. This applied not only to the whole series but also to individual patients whose test results might change from time to time, sometimes following treatment, at others apparently spontaneously. It seems difficult to envisage these fleeting deviations from the normal as the essential cause of so definite and constant a symptom as hemorrhage. Hemorrhage might on the other hand have resulted from intravascular thromboses, themselves the effect of thrombocytosis, as suggested by Soulier et al. The primary lesion might be infarction; once bleeding had started, it might then be aggravated by any functional platelet abnormality or deficit of coagulation factors which happened to be present. Anlotti and Ballerini suggested multiple capillary thrombi with a consequent excessive consumption of fibrinogen and lowering of the fibrinogen level as being responsible for the bleeding. There is as yet little pathologic evidence to support these otherwise very plausible suggestions. Meanwhile the bleeding tendency in hemorrhagic thrombocythemia remains a still unexplained puzzle.

Treatment

The tendency for untreated patients with hemorrhagic thrombocythemia is gradually to deteriorate in health and to die eventually of their complaint.
Even in mild cases there are usually repeated periods of ill health. Relatively few patients with the disorder have been treated, but there is no doubt that appropriate therapy is of the greatest benefit. In such a therapeutic regimen splenectomy is absolutely contraindicated since it invariably aggravates the hemorrhagic manifestations.

Radioactive phosphorus ($^{32}$P) has on the other hand been found to be of as much value in this disorder as it is in polycythemia vera.$^{76}$ It lowers the platelet and leukocyte count within two or three weeks and either reduces the red cell level or leaves it unaffected. As the platelet count falls, the hemorrhages diminish and eventually cease, and judicious repetition of the same or reduced doses of the isotope can maintain a normal platelet level and clinical state for long periods. $^{32}$P was used successfully in cases 2 and 3 of the personal series, and in several patients in the literature.$^{9,21,23,38,72,74,78}$ One patient received combined treatment with urethane and x-rays to the skeleton,$^{74}$ also with satisfactory results. In cases 2 and 4 of the personal series busulphan (Myleran) was employed as an alternative to $^{32}$P and with equal success. This drug was given continuously, as in the treatment of chronic granulocytic leukemia, and very steady platelet and leukocyte levels were maintained, with a complete absence of symptoms.

It is concluded that whenever high platelet counts are found to be associated with excessive bleeding, treatment by radiotherapy or chemotherapy should be initiated without delay, since the chances of worthwhile remissions in the symptoms are excellent and no relief is likely in the absence of therapy.

**Conclusions**

1. Hemorrhagic thrombocythemia is a clinical syndrome characterized by excessive bleeding and extremely high platelet counts, usually associated with other clinical and hematologic abnormalities.

2. Though hemorrhagic thrombocythemia has no individual pathologic findings which could designate it as a "primary" disease, and though it is closely related to such members of the myeloproliferative disorders as polycythemia vera and myelosclerosis with myeloid metaplasia, its clinical and hematologic manifestations as well as prognosis are distinctive. It is suggested that hemorrhagic thrombocythemia and polycythemia vera be regarded as divergent forms of an underlying myeloproliferative disorder.

3. The mechanism of the excessive bleeding has not been satisfactorily explained.

4. Splenectomy is contraindicated in hemorrhagic thrombocythemia. Treatment with radiophosphorus or chemotherapy is of value and should always be given.

**Summario in Interlingua**

1. Thrombocythemia hemorrhagic es un syndrome clinic que es characterisate per sanguination excessive e altissime numerationes plachettal. Illo es usualmente associate con altere anormalitates clinic e hematologic.
HEMORRHAGIC THROMBOCYTHEMIA: A CRITICAL REVIEW

2. Ben que thrombocythemia hemorrhagic non se distingue per constata-
tiones pathologic individual que permiterea designar lo como morbo primari
e ben que illo es intimemente relationate con entitates in le gruppo del dis-
ordines myeloproliferative como per exemplo polycythemia ver e myelosclerosis
con metabolis myeloide, su manifestationes clinic e hematologic e etiam su
prognose es de character distinctive. Es proponite que thrombocythemia hemor-
rhagic e polycythemia ver es reguardate como divergente formas de un sub-
jacente disordine myeloproliferative.

3. Les mechanismo del excessive sanguination ha non ancora trovate tin
explication satisfactoni.

4. Splenectomia es contraindicate in thrombocythemia hemorrhagic. Tracta-
mento con radiophosphoro o chimotherapia es de valor e deberea esser usate
in omne casos.

REFERENCES


path. Anat. 103:95, 1939.

3. Arlotti, O., and Ballerini, G.: La pato-
genesis delle sindromi emorragiche e
trombotiche nelle trombocitemie. Hae-

and thrombocytosis in the myelopro-
liferative syndromes. Scot.M.J. 3:26,
1958.

5. Baserga, A., Arlotti, O., and Ballerini,
G.: Deux cas de thrombocytémie avec diathèse hémorragique au cours
de la maladie de Vaquez. Sang 28:
218, 1957.

in blood. Measurements in normal sub-
jects, in patients with thrombocythe-
emia hemorrhagica, and other hemor-
rhhagic states. J.Lab.& Clin.Med. 43:
759, 1954.

7. Binswanger, D., Schaub, F., and Scheit-
lin, W.: Zur hämorrhagischen Diathese
bei extremer Vermehrung der Throm-
bozyten (Thrombocythaemia hämor-

8. Boros, J. von: Über einen Fall von
akuter Megakaryoblastenleukämie, zu-
gleich einige Bemerkungen zum Pro-
blem der akuten Leukämie. Zschr.klin.

9. Bousser, J.: Thrombocythémie dite es-
sentielle (avec polyglobulie). Sang

10. Brugsch, H.: Persistierende Thrombo-
cythämie und Leukämie nach Milzent-
fernungs. Folia haemat. 49:454, 1933.

11. Dameshek, W.: Some speculations on
the myeloproliferative syndromes.

12. —, and Gunz, F.: Leukemia. New

13. —, and Henstell, H. H.: The diagnosis
1360, 1940.

14. D’Antuono, G.: Le trobocitemie. Hae-

15. Di Guglielmo, G.: Megacariociti e pia-

16. Drake, C. B.: Leukemia with thrombo-

17. Epstein, E., and Goedel, A.: Hämor-
rhagische Thrombocythämie bei vascu-
293:233, 1934.

18. Epstein, J. A., and Richter, I. H.,
Essential thrombophiliia: report of a

19. Fanger, H., Celia, L. J., Jr., and Litch-
man, H.: Thrombocythemia: report of
three cases and review of literature.

20. Forssell, J.: Epikris till ett fall af poly-
cytemi, anemi och forkalkad mjälte
hos samma patient. Nord.Med. 33:313,
1947.

21. Fountain, J. R.: Haemorrhagic throm-
bocythaemia. Report of two cases
treated with radioactive phosphorus.

22. Gormsen, J.: A technique for the hepar-
in-tolerance test. Brit.J.Haemat. 5:
HEMORRHAGIC THROMBOCYTHEMIA: A CRITICAL REVIEW

and Goglin, G.: Deux cas de spléno-mégakaryocyte myéloïde avec thrombo-

cythémie hémorragique. Action du myélorétro. Intérêt des thrombo-élasto-


51. Manpin, B., Baylon, H., Moras, P.,

and Vigne, J.: Sur un cas de thrombo-

cythémie hémorragique évoluant au

cours de la maladie de Vaquez. Sang


52. Mittus, W. J., Bergna, L. J., Mednicoff,

I. B., and Dameshek, W.: Alkaline

phosphatase of mature neutrophils in

chronic forms of the myeloproliferative

syndrome. Am.J.Clin.Path. 30:


53. Monto, R. W., Griest, W. D., and

Szilagyi, D. E.: Essential thrombo-

philia. A.M.A.Arch.Int.Med. 90:54,

1952.

54. Moolten, S. E., Vroman, L., Moolten,

G. M. S., and Goodman, B.: Role of

blood platelets in thromboembolism.


55. Mortensen, O.: Thrombocytèmie hem-

orrhagica. Acta med.scandinav. 129:

547, 1948.

56. Niles, N. R., Koler, R. D., Johnson, R.

L., Smith, D. D., and Dunlap, W. J.: Myeloproliferative
diseases. Clinical and pathologic study of

69 cases. Am.


57. Nygaard, K. K., and Brown, C.:


58. Owren, P., Thrombocytémie essentielle.


59. Page, I. H.: Serotonin (5-hydroxytrypt-

tamine); the last four years. Physiol.


60. Paraf, A., Colonna, D., and Caroli,

J.: Pyléphlébite thrombocythémique.


Lancet 2:548, 1940.

62. Revol, L.: La myélose hyperthrombo-

63. Rosenthal, N.: Clinical and hematologic

studies on Banti's disease. 1. The

blood platelet factor with reference to

splenectomy. J.A.M.A. 84:1887,

1925.

64. Rowlands, R. A., and Vaizey, J. M.:

Primary thrombocythaemia. Lancet 2:

1217, 1938.

65. Schulpach, A., and Herrmann, E.: Thrombosekrankheit bei essentieller

(?) thrombocythaemia. Schweiz.med.

Wscr. 84:95, 1954.

66. Siele, W.: Hämorrhagische Diathese und


67. Smith, M. D.: Essential thrombocytosis

and its significance: with report of a


68. Sünderström, N.: Om hämorrhagisk trom-


69. Soulier, J. P., Alagille, D., and Larrieu,

M. J.: Physiopathology des hémor-
gragies au cours des hyperplaquettoses.

Etude de l'hémostase chez 27 malades.


70. —, Larrieu, M. J., and Wartelle, O.: La

thromboplastino-formation dans les

affections plaquettaires. Étude de 34
cas à l'aide du test de Biggs et Doug-


71. Spaet, T. H.: Anticoagulant effect of

excess platelets (abstract). J.Clin.In-


72. —, Bauer, S., and Melamed, S.: Hemor-

rhagic thrombocythemia. A blood co-

agulation disorder. A.M.A.Arch.Int.


73. Spangberg, J., and Zettergren, L.: A

case of thrombocythemia essentialis.


74. Stenström, N. M.: Three cases of mega-

karyocytic leukemia. Acta med.scand-


75. Thicifry, S., Buhot, S., and Aicardi, J.: Une

observation de thrombocythémie


76. Tubiana, M., and Boiron, M.: Le traite-

ment des thrombocytémies par le

phosphore radio-actif. Sang 28:291,

1957.

77. Uotila, U.: On hemorrhagic thrombo-

cythemia. Acta med.scandinav. 95:136,

1938.

78. Wasserman, L. R., Vroman, L., and

Gelin, G.: Hémorragies et thromboses

au cours de la thrombocythémie es-

sentielle (à propos de 3 observations


79. Woodrow, J. C., and Cope, S.: Haemor-

rhagic thrombocythaemia treated with

radioactive phosphorus. Brit.M.J. 2:

1069, 1955.

80. Zucker, M. B., and Borrelli, J.: Concen-

tration of serotonin in serum in

thrombocytopathia, pseudo-hemophilia


26:13, 1956.
Hemorrhagic Thrombocytethemia: A Critical Review

F. W. GUNZ